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MINI-REVIEW ARTICLE

Fungal Endophytes: A Storehouse of Bioactive Compounds

Suraj Kumar Shah[1], Yadu Nandan Dey[2], Yasasve Madhavan[3] and Arindam Maity[4,*]

[1]Department of Pharmaceutical Technology, School of Medical Science, Adamas University, Kolkata-700126, West Bengal, India; [2]Department of Pharmacology, Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur-713206, West Bengal, India; [3]Sree Sastha Institute of Engineering and Technology, Chennai - Bangalore Highway, Chembarambakkam, Chennai-600123, Tamil Nadu, India; [4]Department of Pharmaceutical Technology, JIS University, Kolkata -700109, West Bengal, India

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Abstract: Fungal endophytes are the microbial adaptations that usually enter the plant tissues during their life cycle without harming the host plants. They are found everywhere on earth and generally depend on the hosts by developing various symbiotic relationships, like mutualism, hostility, and parasitism on rare occasions, leading to the growth and rise in the nutrient content of the hosts. Endophytes can develop tolerance in host organisms against the stresses induced by either living or non-living agents. They may protect them from insects or pests by building resistance. Interestingly, endophytes can synthesize many phytohormones, natural medicinal compounds and several essential enzymes beneficial for biotechnological perspectives that can be obtained by culturing plant tissue in a suitable medium. These endophytes are a reservoir of many new active phytoconstituents, like alkaloids, phenolics, steroids, quinones, tannins, saponins, *etc.*, which exhibit anticancer, anti-insecticidal, antioxidant, antibacterial, antiviral, antifungal, and many more properties. Exploring the new bioactive chemical entities from the endophytes may supply potent lead compounds for drug discovery to combat numerous disease conditions. Hence, the present review was carried out to explore the significance of the fungal endophytes and their medicinal, food, and cosmetic use.

Keywords: Endophytes, bioactive compounds, phytohormones, secondary metabolites, drug discovery, fungal endophytes.

1. INTRODUCTION

Plants are the vital source of many bioactive substances that have been utilized to cure a variety of ailments since antiquity. In contrast, microorganisms associated with plants have also offered many important therapeutically potent products [1]. Among them, fungal endophytes are the microbial adaptations that usually take place in plant tissues during their life cycle without causing any harm to the host [2]. An endophyte depends on the hosts by developing various symbiotic relationships, like mutualism, hostility, and parasitism on rare occasions that derive nutrients from the host [3]. On the contrary, it promotes the growth of the host plant and enhances its survival potency by synthesizing and altering the metabolic pathways, thus leading to the production of many essential secondary metabolites and enzymes [4]. Interestingly, endophytes can synthesize many phytohormones and natural medicinal compounds as well as several important enzymes beneficial for biotechnological perspectives that can be obtained by culturing plant tissue in a suitable medium [5].

*Address correspondence to this author at the Department of Pharmaceutical Technology, JIS University, Kolkata-700109, West Bengal, India; E-mail: arindam.ju05@gmail.com

As indicated by the researchers, every single plant studied to date has one or more types of endophytes in it [6]. The colonization of endophytes is found in various components of the plants, like stem, root, petiole, leaf, inflorescence, fruit, seed, and also dead hyaline tissue [7-9]. Their growth in host organisms is primarily governed by factors, such as host species and developmental stage, inoculum density, and environmental condition, and thus is highly variable [10].

The exploration of these important fungal endophytes and their phytochemical content is limited to very few relevant studies. The rate of development of new compounds from endophytes-host interaction has declined because modern herbal drug discovery only focuses on the isolation and development of bioactive molecules from the plant, which shows beneficial effects in many diseases. However, fungal endophytes show a crucial contribution to the development and modification of new natural products for curing chronic diseases, leading to the dissemination of their use in herbal drug development [11]. Exploring the newly discovered bioactive chemical entities from the endophytes may supply major potent lead compounds for drug discovery to combat numerous disease conditions. Hence, in the present review, we explored the significance of the fungal endophytes and their medicinal, food, and cosmetic use.

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This will enable us to understand the importance of endophytes and address the need for the development of novel bioactive pharmacophores using fungal endophytes, which may be essential to fight against several disease-causing pathogenic organisms in humans. It will also help explore the other medicinal properties of the phytoconstituents and enzymes, which are produced by endophytes in the host organism.

2. UNDERSTANDING ENDOPHYTE

Numerous surveys, studies, and several explanations suggest very little involvement of pathogenic microorganisms in plants [12]. The majority of the microbes are involved in the growth and development of the plant, while few of them show neutral effects [13]. The microorganisms involved in a symbiotic relationship with plants may be classified into epiphytes and endophytes based on the colonization site of the plant. Epiphytes are the microbial populations that exist on the surface of plant parts, while the endophytes reside within the plant tissues in various parts, *i.e.*, leaf, root, or stem [12, 14-15].

In 1866, De Bary first observed the existence of non-pathogenic microbes apart from disease-causing microbes inside plants. De Bary identified the presence of the microbes in the plant tissue by microscopic analysis. De barry (1866) stated the definition of endophytes as "*any organism that grows within plant tissues and is termed as endophytes.*" However, the definition of endophyte termed by different scientists may vary [16-19]; the appropriate definition was coined by Petrini [1991], which states that endophytes are the type of microorganisms that form colonization inside the host plant tissue without harming them [20]. Various studies have revealed that these microbes lead to the division of endophytic populations into different subcategories, like obligate or facultative, that exist in all types of plants [21]. Obligate endophytes are the type of endophytes that depend on the metabolism of plants through acting on various vectors or vertical transmission [22], while the facultative endophytes reside outside the host organism till a specific time and are mostly connected with the host from its neighboring soil atmosphere [23].

Researchers assessed the genome size and origin of endophytes by relating them with the genome size of bacteria [24]. The endophytic community is made up of organisms from various origins, with bigger genomes living in a more changeable environment, such as dirt, and smaller genomes living in a more stable environment and being vertically transmitted [25].

3. TYPES OF ENDOPHYTES

Endophytes mainly constitute bacteria or fungi, which form colonies inside the plant tissues and are associated with plants in diverse forms. Bacterial endophytes are comprise Achromobacter, Agrobacterium, Bacillus, Brevibacterium, Microbacterium, Xanthomonas, Pseudomonas, and other gram-positive and gram-negative bacteria [26 a, b]. Bioactives that exhibit antibacterial and anticancer properties are produced by a vast collection of bacterial endophytes, with 76% of those described as Streptomyces [27]. Fungi act as heterotroph organisms with symbiotic connections with a wide range of autotrophic creatures [28].

Fungal endophytes are divided into Clavicipitaceous and non-Clavicipitaceous endophytes based on their phylogeny and life cycle features. The Clavicipitaceous endophytes affect a few types of grass in a cool environment. In contrast, the non-Clavicipitaceous endophytes are commonly found in asymptomatic tissues of non-vascular plants, conifers, angiosperms, fern, and fern allies, and are limited to the Basidiomycota or Ascomycota groups [29, 30].

Some of the most widely used antibiotics and anticancer medicines are made by the endophytic fungus. Several cell lines are cytotoxic to penicillenols, isolated from penicillium sp. Taxol, derived from the endophytic fungus Taxomycesadreanae, is the most potent and successful anticancer medication ever discovered. Clavatol (Torreyamairei), sordaricin (Fusarium sp.), jesterone (Pestalotiopsisjesteri), and javanicin (Chloridium sp.) have been reported to have antibacterial and antifungal effects with high potency against a wide range of food-borne pathogens [29]. Pestacin, derived from *P. microspora*, is a powerful antioxidant.

4. METHODS FOR SCREENING FUNGAL ENDOPHYTE

Fungal endophytes produce a range of bioactive secondary metabolites having distinct structures, including alkaloid, flavonoid, quinone, steroid, terpenoid, and other chemicals [31a]. The antibacterial, antifungal, antiviral, immunomodulatory, antioxidant, and antineoplastic properties of these compounds have a wide range of applications [31 b, c]. These bioactive metabolites are known to have various pharmacological applications, such as antibacterial, antifungal, antiviral, immunomodulatory, antioxidant, and antineoplastic [32-35]. Besides the different biological activities, fungal endophytes are also useful for different applications in agricultural sectors [36-38]. The traditional approaches to screening fungal endophytes include bioactivity-guided fractionation to isolate the bioactive constituents and further purification by modern analytic techniques to identify and characterize the lead compounds. The isolated endophytic fungus is cultivated and subjected to extraction with several organic solvents to produce these metabolites commercially. The whole extract is then put through a series of steps, including biological activity testing by using various pharmacological models. The biologically active compounds are further purified from the bioactive extracts [39-45].

Molecular identification of the bioactive chemicals is done using a combination of spectroscopic techniques and precision chromatographic equipment. Several secondary metabolites, including bioactive substances, have chemical structures, and spectroscopic data are available in databases, such as the Human Metabolome Database (HMDB) [46], the METLIN database [47], and the Madison Metabolomics Consortium Database (MMDB) [48]. By comparing the spectroscopic data available in databases, these substances can be identified. Several spectroscopic techniques, such as molecular ion mass spectrometry and fragmentation pattern, can be utilized to detect a number of unidentified substances for which data are lacking [49, 50]. Such data are also generated using tandem mass spectroscopy and liquid chromatography systems [51]. The data generated *via* nuclear magnetic resonance and infrared spectroscopy also provide important information about the chemical structure of unknown compounds, which aids in the elucidation of their molecular structures [52, 53]. The isolation of fungal endophytes using these traditional methods was time-consuming and prone to mistakes. As a result, efficient screening approaches for a large number of isolated fungal endophytes to identify fungal strains capable of synthesizing certain novel pharmaceutically essential chemicals are required.

4.1. Genome Mining to Screen Fungal Endophyte

The search for novel bioactive compounds has driven researchers to mine the entire genome sequence to find metabolic routes for previously undiscovered metabolites. This information was "finished out" of DNA libraries to uncover gene clusters and new natural products for known metabolites [54]. There are many more gene clusters for secondary metabolite manufacturing in the filamentous fungal genome than previously estimated compounds. Signature genes or enzymes encode various secondary metabolites, including non-ribosomal peptide synthases, terpene synthases, and polyketide synthases. These genes are thought to be the originators of the secondary metabolic gene cluster. These genes (for example, acyltransferases, oxidoreductases, glycosyltransferases, and methyltransferases) are also responsible for tailoring enzymes that modify the skeleton of secondary metabolites [55a]. Genome mining of Aspergillus spp. indicated the presence of roughly 40 cryptic secondary metabolite biosynthetic gene clusters per genome. The secondary metabolic gene clusters in filamentous fungus are under conventional laboratory conditions, resulting in no product formation. Gene mining will boost the production of derivatives with possibly higher characteristics for synthesizing bioactive chemicals by fungal endophytes [55b].

4.2. Screening of Fungal Endophyte Using Molecular Marker

A specific enzyme expressed by the appropriate gene catalyzes the numerous steps in a biosynthetic pathway. After collecting the essential genes for encoding various enzymes, an organism can use these enzyme catalysis mechanisms to generate a specific metabolite. As a result, significant genes encoding crucial enzymes in that biosynthetic pathway could serve as a marker for these fungal endophytes' ability to synthesize those compounds [56]. The biosynthesis process of paclitaxel (Taxol) and similar taxanes has been thoroughly studied, and the genes encoding these enzymes have been cloned [57 a, b]. Such screening will cut down on screening time and increase efficiency.

5. MOLECULAR CHARACTERIZATION AND IDENTIFICATION OF FUNGAL ENDOPHYTES

The various fungi from which fungal endophytes originate are Basidiomycota, Zygomycota, and Ascomycota. Identifying the specific type of fungal endophyte in the isolated material depends on their characteristic feature to produce spores in the nutrient media (Fig. **1**). The traditional fungal classification relies primarily on reproducing structures; the non-sprouting fungi cannot be provided with taxonomic names [58]. Molecular tools applications, such as sequencing methods and DNA fingerprinting, illustrate the ability to overcome traditional taxonomic challenges for cultivable fungus. In fungal endophytes, 5.8S gene and flanking Internal Transcribed Spacers (ITS1 and ITS2) of the rDNA, 18S, and 28S rRNA genes have been employed to identify fungal endophytes (Fig. **2**). Based on ITS sequence analysis, Pandey *et al.* identified distinct isolates of Phyllosticta isolated from diverse tropical tree species in India as P. capitalensis [59]. On the basis of ITS sequence similarity and phylogenetic analysis, Sun *et al.* classified 221 non-sporulating endophyte strains into 56 morphotypes and 37 taxa. Despite certain limitations in species differentiation, the ITS region is the most extensively utilized DNA barcode in endophytic fungus for molecular identification [60].

6. BIOACTIVE COMPOUNDS FROM ENDOPHYTE

Previous reports have revealed that the several bioactive metabolites produced from endophytes are a rich source for treating various diseases. They have wide applications in agricultural, medical, food, and cosmetic sciences [5, 29, 61, 62]. Fungi also remain a rich source of many therapeutic agents. The identification and isolation of many pharmaceutically important substances are obtained from fungal endophytes. Fungal endophytes are also supposed to be a novel source of bioactive compounds, and hence, many studies have been carried out to isolate and identify bioactive constituents of endophytes (Fig. **3**). Fungal endophytes maintain a systemic relationship with the host organism and protect it from pathogenic microorganisms [29]. Nowadays, the endophytes are extensively valuable tools to control many plant diseases, which is very fruitful for the yield. This is an emerging area for research in various industrial applications. The potent ecological role of some of the secondary metabolites produced from the endophytes has been emphasized. The examples of bioactive constituents produced by fungal endophytes are illustrated in Table **1** along with their relevant activity discovered.

6.1. Fungal Endophyte as a Source of Anticancer Compound

Uncontrolled cell proliferation in any part of the body is known as cancer, leading to death if untreated. Cancer is one of the major causes of death worldwide. Anticancer drugs cause numerous adverse reactions and toxicities to the normal proliferating cells. Cancer treatment is improved due to better diagnostic-based treatment, which allows medical professionals to detect the condition early and proceed with more precise treatment procedures. Previous reports reveal that the endophyte-derived bioactive compounds are potent anticancer agents, which suggests that the approach of developing novel drugs by using endophytes may be a good alternative [66]. The bioactive anticancer compounds derived from endophytes are depicted in Table **1**.

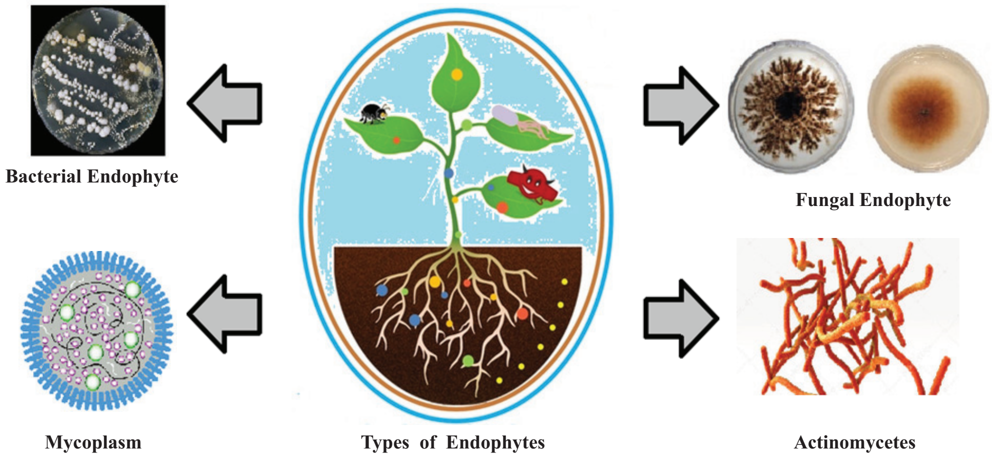

Fig. (1). Types of endophytes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

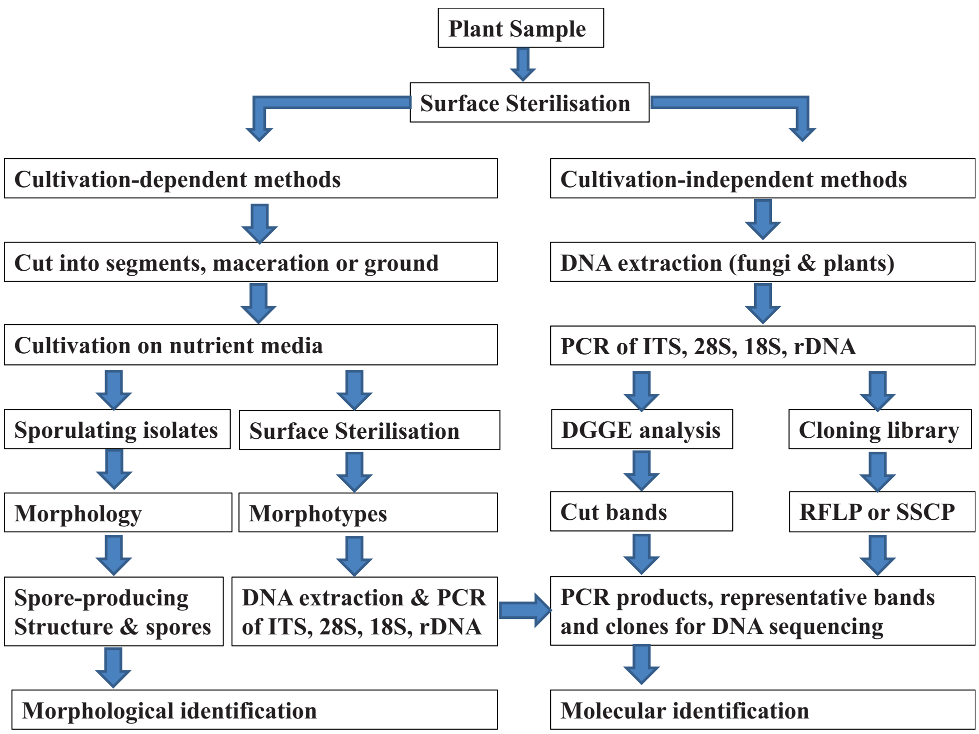

Fig. (2). Steps of isolation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

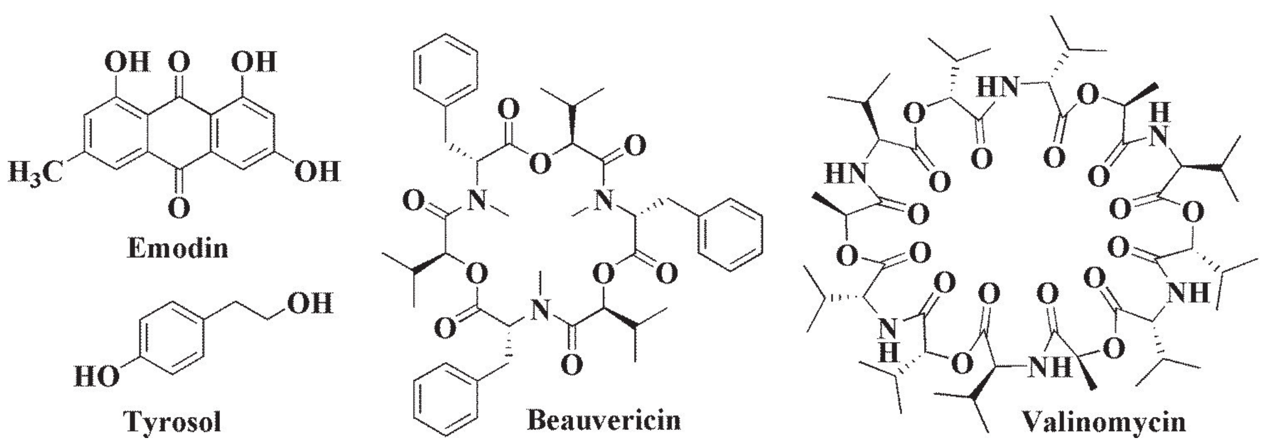

Fig. (3). Structure of tyrosol, beauvericin, and valinomycin (bioactive endophytes).

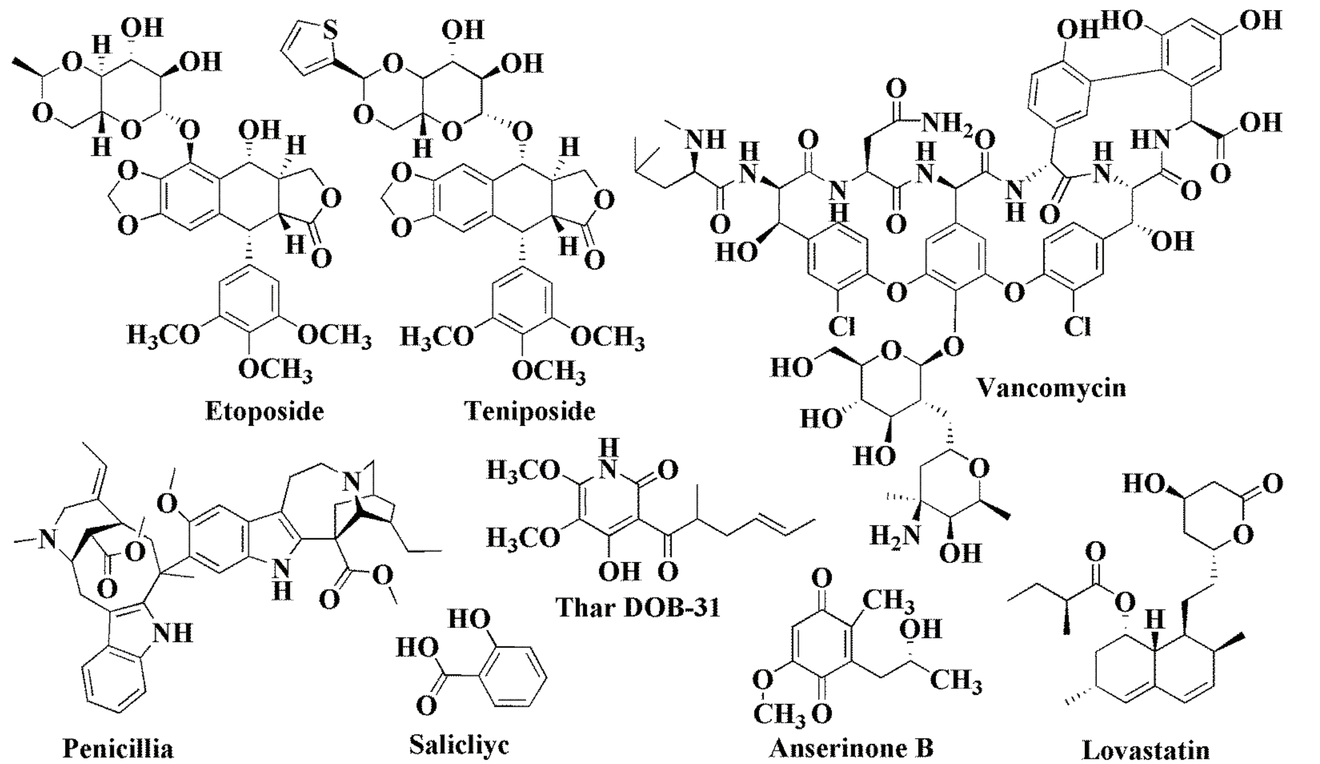

Fig. (4). Podophyllotoxin and other endophytes derivatives.

Table 1. Bioactive compounds obtained from the different fungal sources (Fig. 4).

Bioactive Compound	Fungal Source	Activity/Application	Refs.
Penicillia	*Penicillium. Sp*	Pain control	[30]
Salicyclic	*Salix sp (willow)*	Analgesic, Anti-inflammatory	[30]
Lovastatin	*Aspergillus terreus*	Cholesterol lowering agent	[30]
Vancomycin	*Nocardia orientalis*	Antibiotics	[30]
Thar DOB-31	*Trichoderma harzinum*	Antimicrobial	[63]
MC-14 L (Extract)	*Fusarium oxysporum*	Antimicrobial	[64]
MC-24 L (Extract)	*Cladosporium tenuissimum*	Antimicrobial	[64]
Anserinone B	*Alternaria sp*	Anti-cancer	[65]

The discovery of taxol was a breakthrough in cancer treatment. Taxol has been utilized in the treatment of advanced lung cancer, breast cancer, and ovarian cancer. Taxol is isolated from fungal endophyte *Taxomyces andreanae*. The procedure is very cost-effective, and the drugs are produced *via* microbial fermentation. Taxol has been found to be present in various plants as well as endophytes (Fig. **5**) [67].

Camptothecin alkaloid is one of the chief constituents found to be effective in treating cancer, which is isolated from the woods of Camptotheca acuminate, widely distributed in China. The biomarker compounds present in the plant are camptothecin and 10-hydroxycamptothecin, which are used as antineoplastic drugs. The derivatives of camptothecin have been found to have very high medicinal values without exhibiting any adverse effects or drawbacks [68]. Hence, the separation and refining of camptothecin and its derivatives from the fungal endophytes will be highly productive and beneficial for the treatment of cancer patients. The two derivatives of camptothecin,

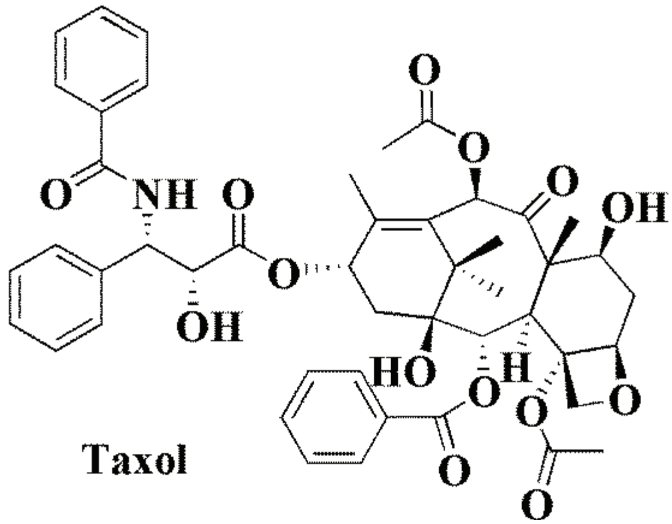

Fig. (5). Structure of taxol.

Table 2. Podophyllotoxin obtained from different endophytic fungi (33 a, b).

Endophytic Fungus	Fungal Strain	Host Plant	Podophyllotoxin Content or Yield
Trametes hirsuta	-	*Sinopodophyllum hexandrum*	30 µg/g
Phialocephala fortinii	PPE5, PPE7	*Sinopodophyllum peltatum*	0.5–189 µg/L
Penicillium sp.	-	*Sinopodophyllum hexandrum*	-
Penicillium sp.	-	*Diphylleia sinensis*	-
Penicillium sp.	-	*Dysosma veitchii*	-
Penicillium implicatum	SJ21	*Diphylleia sinensis*	-
Penicillium implication	2BNO1	*Dysosma veitchii*	-
Monilia sp.	-	*Dysosma veitchii*	-
Fusarium oxysporum	JRE1	*Sabina recurva* (*Juniperus recurva*)	28 µg/g
Alternaria sp.	-	*Sinopodophyllum hexandrum* (*Podophyllum hexandrum*)	-
Alternaria neesex	Ty	*Sinopodophyllum hexandrum*	2.4 µg/L

viz., 9-methoxycamptothecin and 10-hydroxycamptothecin are derived from *Fusarium solani* (a fungal endophyte), which is isolated from *Camptotheca acuminate* [67-70]. Few other studies have revealed the isolation of other analogs of camptothecin-producing endophytes [71]. Subsequently, the studies on the endophytes have tremendously increased to develop newer agents from the fungal products.

Podophyllotoxin and its derivatives have been proven to have cytotoxic properties, which suggest that they have high efficacy as anticancer drugs, like etoposide, teniposide, and etopophos phosphate [72 a, b]. Podophyllotoxin is a phytoconstituent that is obtained from *Podophyllum* sp. As the species is known to be classified as an endangered category, research to find more alternate sources for podophyllotoxin and its derivatives should be focused. The previous study identified Trametes hirsute (fungal endophyte), which is capable of synthesizing podophyllotoxin and its derivatives, *i.e.*, aryl tetralin lignans, with potent anticancer activities [69]. The different strains of endophytic fungi producing podophyllotoxin are represented in Table **2**.

Ergoflavin is a dimeric xanthene belonging to a structured group termed ergochromes. Ergoflavin has been reported to have anticancer properties purified from a fungal endophyte associated with the leaves of *Mimusops elengi* (Sapotaceae) [73]. Another anticancer drug is secalonic acid D, a mycotoxin, categorized as ergochrome class. Secalonic acid was reported to be purified from the mangrove endophytic fungus and found to have high cytotoxicity on K562 and HL60 cells by triggering leukemia cell apoptosis [74].

When compared to DMSO-treated cells, crude extracts of *Alternaria alternata*, an endophytic fungus isolated from Coffea arabica L., showed modest cytotoxic activity against HeLa cells *in vitro* [75]. In an investigation of endophytic actinomycetes linked with medicinal plants in the rainforest, Li *et al.* reported 41 compounds from the genus Streptomyces to have considerable anticancer activity against HL-60 cells, A549 cells, BEL-7404 cells, and P388D1 cells [76 a, b].

6.2. Fungal Endophytes as a Source of Antioxidant Compounds

Antioxidants have recently piqued researchers' interest. The topic of free radical chemistry is currently gaining popularity. Free radicals are oxygen and nitrogen reactive species produced by various physiological activities in the body. Uncontrolled production of free radicals causes oxidative stress and, eventually, cell death by attacking membrane lipids, proteins, enzymes, and DNA. Many studies imply that endophytes' metabolites are responsible for the presence of natural antioxidants in medicinal plants, fruits, and vegetables.

Polysaccharides obtained from plants and microorganisms have been extensively studied and these are considered as natural antioxidants. Fungal endophyte also produces antioxidant metabolites, such as isopestacin and pestacin, isolated from *Terminalia morobensis* and *Pestalotiopsis microspore,* respectively. The antioxidant activity of isopestacin is due to its structural similarity to flavonoids, and the activity of pestacin is due to the cleavage of an unusually reactive C-H bond to a lesser extent through O-H abstraction [77]. Literature suggests that the leaves of selected Nigerian ethnomedicinal plants exhibit promising antioxidant activity [78].

Still, several efforts have been made to estimate the total number of fungi associated with plants. The magnitude of fungal diversity is estimated at about 1.5 million (more accurately 1.62 million) species, which has been later revised to 2.27 million [26b, 79]. The research progression on antioxidant compounds produced by endophytic fungi from various medicinal plants is discussed in Table **1**.

6.3. Fungal Endophytes as a Source of Antibiotics

The first secondary metabolite, isolated and differentiated for industrial application, was obtained from fungi [80]. Some of them, like mycotoxins, are harmful, but most are beneficial as antibiotics to humanity [61]. According to fungal mycologists, secondary metabolites play an important role *in vivo*, and are essential for many metabolic interactions between their plant host and fungal hosts, such as maintaining signaling, regulation, and defense of the symbiosis.

6.3.1. Antibacterial Agents

The endophytes isolated from medicinal plants, like *Streptomyces* sp., are bioactive against several tested microorganisms. Over 70% of the world's antibiotics are obtained from streptomycetes. Secondary metabolite production is strictly regulated and controlled. The development of novel endophyte antimicrobial metabolites is an effective alternative to overcoming rising levels of plant and human pathogens' drug resistance, inadequate numbers of successful antibiotics against different bacterial organisms, and few new emerging antimicrobial agents, possibly due to comparatively unfavorable investment returns [81, 82].

In recent decades, the rise of multidrug-resistant (MDR) microorganism infections has gotten much attention [83, 84]. Drug-resistant microorganisms and infectious diseases are becoming a huge challenge. One of the most pressing issues in modern medicine is antibiotic resistance [85]. New issues necessitate the development of new antibiotics derived from fungi. Current antibiotics have developed resistance in Staphylococcus aureus (MRSA) and Vancomycin-resistant Enterococcus faecium (VREF). Antibiotics are no longer useful in the treatment of human disease due to antibiotic resistance. In this circumstance, old medicines must be replaced with new pharmaceuticals [86]. Endophyte metabolites have been shown to suppress the growth of microorganisms in the host. Fungal endophytes with new metabolites are physiologically active against a variety of resistant human diseases. According to the World Health Organization (WHO), Mycobacterium tuberculosis (MT) infects one-third of the world's human population [87]. The evolution of multi-drug resistance in M. tuberculosis bacteria necessitates the rapid discovery and development of novel, non-toxic treatment medicines derived from natural sources. The antitubercular activity was found in Phomapyrrolidones A-C isolated from Phoma sp. NRRL 46751 [88]. Xia *et al.* discovered Alterporriol-type dimers from Alternaria sp. (SK11), a mangrove endophytic fungus, and found the substance Atropisomer 2 to have potent anti-MT action [89]. Natural chemicals from Annulohypoxylon ilanense of the medicinal plant Cinnamomum species were tested against MT by Ming *et al.* in 2013. Since the discovery of penicillin saved billions of lives and played an important role in human history, it generated more interest in discovering new antibiotics due to the drug resistance to the existing drugs [90]. Thus, recently, there has been an increasing number of articles on the research of endophytes producing antimicrobial and antibacterial substances [91-96 a, b, c] for the search of new antibiotics.

6.3.2. Antifungal Agents

Many bioactive compounds, including antifungal agents, have been isolated from the genus *Xylaria* residing in different plant hosts, such as "sordaricin" with antifungal activity against *Candida albicans;* "mellisol" and "1,8-dihydroxynaphthol 1-O-a-glucopyranoside" with activity against herpes simplex virus type 1; and "multiplolides A and B" with activity against *Candida albicans* [97]. "7-amino-4-methyl coumarin" was found as the bioactive chemical recovered from the culture extracts of the endophytic fungus Xylaria sp. YX-28 was obtained from Ginkgo biloba L. [98]. The compound showed broad-spectrum inhibitory activity against a variety of food-borne and food spoilage microorganisms, including *S. aureus*, *E. coli*, *S. typhia*, *S. typhimurium, S. enteritidis, A. hydrophila, Yersinia sp., V. anguillarum, Shigella sp., V. parahaemolyticus,* and *C. albicans* [99]. Khalil *et al.* isolated 17 endophyte fungi from *A. marina,* and investigated 8 endophytic fungi using ethyl acetate extract; the fungi were found to exhibit strong activity against different pathogenic bacterial and fungal species. Out of 17 endophytes, *Penicillium commune* EP-5 had a maximum improved farm productivity of 192.1 ± 4.04 µg mL^{-1} in the presence of 5 µg mL^{-1} tryptophan with increased root lengths from 15.8 ± 0.8 to 22.1 ± 0.6 [100]. Another recent investigation by d'Errico *et al.* (2021) isolated two major bioactive metabolites, monocerin, and derivative epoxycyclohexenone, which showed promising activity as biocontrol and bioremediation agents [101].

6.3.3. Antiviral Agents

The search for antiviral chemicals in endophytes is still in its early stages. Only a few substances from fungal endophytes have been described as antiviral drugs. The lack of antiviral screening systems is most likely the biggest stumbling block to antiviral compound development. Altertoxins were identified from Alternaria tenuissima QUE1Se, which displayed HIV-1 viral activity [102]. Several hundred endophytic fungal extracts were tested on HIV-1 replication in T-lymphocytes, and four extracts were found to be non-toxic and to have inhibitory activity ranging from 75 to 99%. Three of these extracts were fractionated, with fraction DB-2 completely inhibiting HIV-1 replication at a concentration that was also found to be non-cytotoxic [103]. Antiviral activity was reported against influenza A viral (H_1N_1) [104] of the compounds emerimidine (A, B), emeriphenolicins (A, D), aspernidine (A, B) austin, austinol, dehydroaustin, and acetoxy dehydroaustin for *Emericella* sp. (HK-ZJ), which is isolated from plant *Aegiceras corniculatum.* Endophytic fungus that resides within desert plants is a source of various natural compounds [105], as well as purified coumarins have been found in Calophyllum inophyllum from Alternaria species. Endophytes Aspergillus, Curvularia, Fusicoccum, Guignardia, Muscodor, Penicillium, Pestalotiopsis, and Phomopsis spp. were isolated from Garcinia plants and tested for antiviral activity against Herpes simplex virus type 1 (HSV-1 ATCC VR-260). Out of 582 pure isolates obtained, EF isolated from 81 Thai medicinal plant species having high antiviral activity against HSV-1 [106-107]. Recent studies suggest that few endophytes also act as potential inhibitors of HIV-1 replication. The study showed 55-60% relative inhibition at different concentrations (0.000 064–0.04 µg/mL), and endophytes to act as HIV-1 protease inhibitors [108].

6.4. Fungal Endophytes for Biotransformation

Biotransformation may be termed as the change in chemical structures of the compounds in any living system [109]. Microbial growth, sustenance, and replication depend on the obtainability of proper sources of a reduced supply of carbon used as chemical energy, which is common under normal growing conditions. However, it is known that microorganisms have no constraints on adapting to new conditions and metabolizing diverse global substrates into carbon and nitrogen sources. A molecule may be modified by transforming functional groups with or without carbon skeleton degradation. These improvements contribute to the formation of novel and usable products, which are not readily prepared by chemical methods [110].

The biotransformation of a tetrahydrofuran lignan, (-)-grandisin, by the endophytic fungus *Phomopsis* sp. from *Viguiera arenaria*, was demonstrated by Verza *et al*. [111]. The process led to the formation of a new compound named "3,4-dimethyl-2-(4′-hydroxy-3′, 5′- dimethoxy phenyl)-5-methoxy-tetrahydrofuran", which showed trypanocidal activity similar to its corresponding natural precursor against the causative agent of Chagas disease, the parasite *Trypanosoma cruzi*. Zikmundová *et al*. reported an endophytic fungus isolated from the roots and shoots of *Aphelandra tetragona*, capable of transforming benzoxazinones, 2- benzoxazolinone (BOA) and 2-hydroxy-1,4-benzoxazine-3-one (HBOA), into different series of compounds [112].

Recent studies reveal that active metabolites from fungal endophytes show promising anti-inflammatory, antinociceptive, antiarthritic, and dermo-cosmetic activities [113-115]. Some of the active metabolites found from fungi endophytes having different pharmacological activities are depicted in Fig. (**6**).

7. FUTURE PERSPECTIVE

Fungal endophytes were previously unknown and undervalued in the microbiological world, yet they represent a potential arena for drug development. Thanks to contemporary molecular methods, endophytic fungal biology has evolved into several therapeutic applications. They can now replicate the function and behavior of plants to synthesize secondary metabolites as novel compounds. Bio-fertilizers based on fungal endophyte formulations may be used in the near future to improve soil fertility and agricultural output, as well as medicinal chemistry. Fungal endophytes might be used to break down plastics, electrical materials, and others using rDNA technology. Fungal endophytes can treat cancer, tuberculosis, malaria, diabetes, and other disorders. Fungal endophytes can be used in several fermentation processes to boost the supply of secondary metabolites. A recent study on fungal endophytes at the molecular level might help speed up medication development. With the help of current technologies, fungal endophytic nanoparticles can be used to improve plant growth and health. Endophyte biology, including methods for confirming fungal endophytes

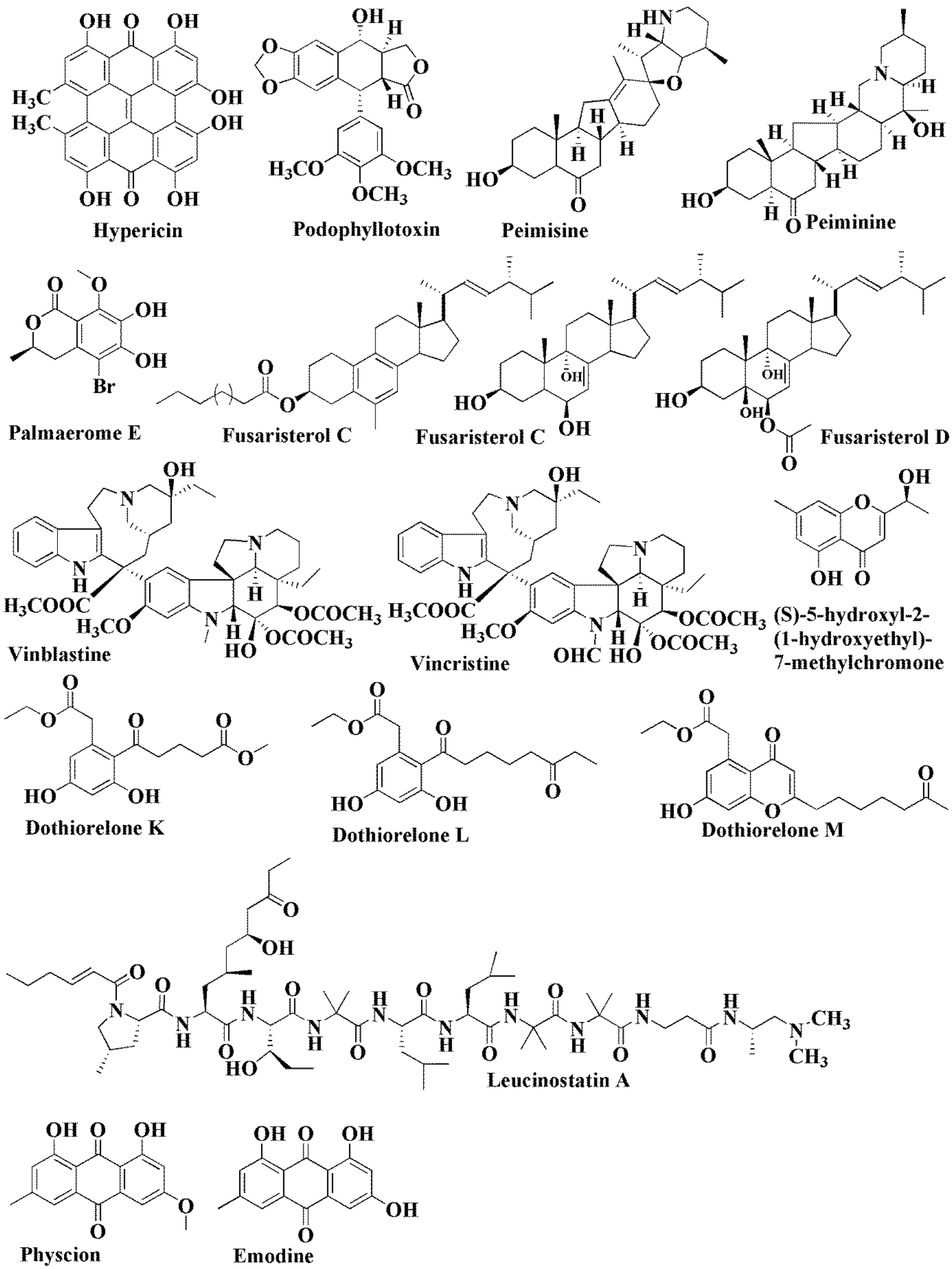

Fig. (6). Different structures of bioactive endophytes.

and separating fungal endophytes from fungal epiphytes, should now be the focus of research.

In the near future, scientists should pay closer attention to the biodiversity of fungal endophytes' functional classes across environmental gradients, how pathogenic endophytes communicate with one another, the mechanisms of plant biogeographic patterns, habitat adaptations, and evolutionary origins, and whether fungal endophytes can be successfully used by rDNA technology.

CONCLUSION

Fungal endophytes are the microbial adaptations inside the host plant tissue that lead to the growth and rise in the nutrient content of the hosts and development of tolerance in the host organism against the different kinds of stresses. Endophytes can also synthesize many phytohormones and medicnal natural compounds, which exhibit anticancer, anti-insecticidal, antioxidant, antibacterial, antiviral, antifungal, and many more properties. Exploring the new bioactive chemical entities from the endophytes may supply potent lead compounds for drug discovery to combat numerous disease conditions. Hence, the present review detailed the importance of endophytes and their application in medicinal, food and cosmetics, and other fields.

LIST OF ABBREVIATIONS

HMDB = Human Metabolome Database

MMDB = Madison Metabolomics Consortium Database

CONSENT FOR PUBLICATION

Not applicable

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None.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

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